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L8: Entry 8 of 14 File: USPT Jun 25, 2002

DOCUMENT-IDENTIFIER: US 6410326 B1
TITLE: Method for inhibiting human tumor cells

Drawing Description Text (47):
FIG. 20 depicts three sites of fusion of HIV env and MOMLV env after site-directed mutagenesis. The joint at the extracellular margin of the transmembrane region is designated as A, while B and C indicate locations of joints at the middle of the transmembrane region and cytoplasmic margin, respectively. The numbering is according to nucleotide numbers (RNA Tumor Viruses, Vol. II, Cold Spring Harbor, 1985). ST, SR, SE are the starts of tat, rev and env while TT, TR, and TE are the corresponding termination sites.

Detailed Description Text (12):
The Xho I site upstream from the ENV gene in the vector provides a convenient site to insert additional promoters into the vector construct as the RSV promoter, SV40 early or late promoter, the CMV immediate early (IE) promoter, human beta-actin promoter, and Moloney murine MLV SL3-3 promoter.

Detailed Description Text (271):
In addition to the gag/pol expressing constructs which begin at nucleotide 563 of MoMLV, several others can be constructed which contain upstream lead sequences. It has been observed by Prats et al. (RNA Tumor Viruses Meeting, Cold Spring Harbor, N.Y., 1988) that a glycosylated form of the gag protein initiates at nucleotide 357 and a translation enhancer maps in the region between nucleotides 200-270. Therefore, gag/pol expressing constructs may be made beginning at the Bal I site (nucleotide 212) or Eag I site (nucleotide 346) to include these upstream elements and enhance vector production.

Detailed Description Text (274):
Envelope proteins from one retrovirus can often substitute, to varying degrees, for that of another retrovirus. For instance, the envelope of murine virus 4070A, HTLV I, GALV, and BLV can each substitute for that of MOMLV, albeit with a lower efficiency (Cone and Mulligan, Proc. Natl. Acad. Sci. USA 81:6349-53, 1984; Wilson et al., J. Virol. 63, 2374-78, 1989; Ban et al., J. Gen. Virol. 70:1987-93, 1989). To increase the number of cell types that could be infected with MLV-based vectors, PCLs were generated which individually express either amphotropic, xenotropic, or polytropic envelopes. Vector produced from any of these PCLs can be used to infect any cell which contains the corresponding distinct receptor (Rein and Schultz, Virology 136:144-52, 1984). Some cell types may, for instance, lack the amphotropic receptor and thus be resistant to infection with amphotropic vector, but express the xenotropic receptor and therefore be infectable by xenotropic vector. One report suggests that xenotropic vector, in the presence of replication-complement xenotropic virus, may more effectively infect human hematopoietic progenitor cells (Eglitis et al., Biochem. Bioiphys. Res. Comm. 151:201-206, 1988). Xenotropic vector, in the presence of replication-competent xenotropic virus, also infects cells from other species which are not easily infectable by amphotropic virus such as bovine, porcine, and equine (Delouis et al.,

Detailed Description Text (277):
Vector produced from the polytropic PCL described herein has a more restricted host

range on human cells than vector produced from either amphotropic or xenotropic PCLs (see data below). The polytropic PCL may therefore be particularly useful for targeting vector to a specific human cell type. The reduced homology between both xenotropic and polytropic envelopes with the MOMLV gag/pol and with the vector makes these PCLs even less likely to generate replication-competent retrovirus by homologous recombination than amphotropic PCLs. Examples of the use of these methods are set forth below (see Example 9).

Detailed Description Text (282):
The most common packaging cell lines used for MOMLV vector systems (psi2, PA12, PA317) are derived from murine cell lines. There are several reasons why a murine cell line is not the most suitable for production of human therapeutic vectors:

Detailed Description Text (287):
The most important safety concern for the production of retroviral vectors is the inherent propensity of retroviral PCLs to generate replication-competent retrovirus after introduction of a vector (Munchau et al., Virology 176:262-65, 1990). This can occur in at least two ways: 1) homologous recombination can occur between the therapeutic proviral DNA and the DNA encoding the MOMLV structural genes ("gag/pol" and "env") present in the PCL (discussed below under "Generation of PCLS"); and 2) generation of replication-competent virus by homologous recombination of the proviral DNA with the very large number of defective endogenous proviruses found in murine cells (Steffen and Weinberg, Cell 15:1003-10, 1978); Canaani and Aaronson, Proc. Natl. Acad. Sci. USA 76:1677-81, 1979; Stoye and Coffin, J. Virol. 61:2659-69 1987). In addition, even murine cell lines lacking vector can produce virus spontaneously or after induction, (e.g., xenotropic virus which can replicate in human cells, Aaronson and Dunn, J. Virol. 13:181-85, 1974; Stephenson and Aaronson, Proc. Natl. Acad. Sci., USA 71:4925-29, 1974; Aaronson and Stephenson, Biochem. Biovhys. Acta 458:323-54, 1976). Another safety concern with the utilization of murine cells for the production of murine retroviral vectors is the observation that some of the many endogenous proviral genes (retrovirus-like genes) in the murine genome are expressed, recognized by the retroviral structural gene products of murine PCLs, and delivered and expressed in target cells with an efficiency at least comparable to that of the desired vector (Scolnick et al., J. Virol. 29:964-72, 1979; Scadden et al., J. Virol. 64:424-27, 1990). These observations strongly suggest that murine cell lines are an unsafe choice for the production of murine retroviral vectors for human therapeutics. To circumvent the inherent safety problems associated with murine cells, PCLs have been generated exclusively from non-murine cell lines (e.g., canine and human cell lines) which are known to lack genomic sequences homologous to that of MoMLV by hybridization analysis (Martin et al., Proc. Natl. Acad. Sci. USA 78:4892-96, 1981). Those skilled in the art will recognize that the packaging cells described herein will have a low, but inherent capability of packaging random RNA molecules. Such RNA moleculse will not be permanently transmitted to the pseudo-infected target cell.

Detailed Description Text (292):
To decrease the possibility of replication-competent virus being generated by genetic interactions between the MLV proviral vector DNA and the structural genes of the PCL, separate expression vectors, each lacking the viral LTR, were generated to express the gag/pol and env genes independently. To further decrease the possibility of homologous recombination with MLV vectors and the resultant generation of replication-complement virus, minimal sequences other than the protein coding sequences were used. In order to express high levels of the MLV structural proteins in the host cells, strong transcriptional promoters (CMV early and Ad5 major late promoters) were utilized. An example of the construction of a MoMLV gag/pol expression vector (pSCV10, see FIG. 19B.1) follows:

Detailed Description Text (294):
2. A 5.3 Kb PstI(partial)/ScaI fragment from the MoMLV proviral plasmid, MLV-K (Miller et al., Mol. Cell Biol. 5:531, 1985) encompassing the entire gag/pol coding

region was isolated.

Detailed Description Text (296):
4. Using linkers and other standard recombinant DNA techniques, the CMV promotor-MoMLV gag/pol-SV40 termination signal was ligated into the bluescript vector SK.sup.+.

Detailed Description Text (320):
Data from the screening process is shown in FIG. 19C. Among the non-murine cell lines which demonstrate the ability to package MoMLV-based vector with high titre are the cell lines CF2, D17, 293, and HT1080. These cell lines were used herein as examples, although any other cells may be tested by such means.

Detailed Description Text (323):
As examples of the generation of gag/pol intermediates for PCL production, D17, 293, and HT1080 were co-transfected with 1 ug of the methotrexate resistance vector, pFR400 (Graham and van der Eb, Virlocry 52:456-67, 1973), and 10 ug of the MoMLV gag/pol expression vector, pSCV10 (above) by calcium phosphate coprecipitation (D17 and HT1080, see Graham and van der Eb, Virology 52:456-67, 1973), or lipofection (293, see Feigner et al., Proc. Natl. Acad. Sci., USA 84:7413-17, 1987). After selection for transfected cells in the presence of the drugs dipyrimidol and methotrexate, individual drug resistant cell colonies were expanded and analyzed for MoMLV gag/pol expression by extracellular reverse transcriptase (RT) activity (modified from Goff et al., J. Virol. 38:239-48, 1981) and intracellular P30.sup.gag by western blot using anti p30 antibodies (goat antiserum #77S000087 from the National Cancer Institute). This method identified individual cell clones in each cell type which expressed 10-50.times. higher levels of both proteins compared with that of the PCL, PA317 (FIG. 19D and Table 3).

Detailed Description Text (330):
Highest titres are obtained when retroviral vectors were introduced into PCLs by infection (Miller et al., Somat. Cell Mol. Genet. 12:175-83, 1986). However, although amphotropic MLV vectors are known to infect these host cell types, the PCLs are blocked for infection by ampho vector since they express ampho env ("viral interference"). To overcome this problem, vectors containing other viral envelopes (such as xenotropic env or VSV G protein, which bind to cell receptors other than the ampho receptor) were generated in the following manner. Ten ug of the vector DNA of interest was co-transfected with 10 ug of DNA which expresses either xeno env (pCMVxeno, above) or a VSV G protein expression vector, MLP G, onto a cell line which expresses high levels of MoMLV gag/pol such as 2-3 cell (see above). The resultant vector containing xenotropic env or VSV G protein, respectively, was produced transiently in the co-transfected cells and after 2 days cell free supernatants were added to the potential PCLs, and vector-infected cells were identified by selection in G418. Both types of vector efficiently infected the ampho-blocked cells and after G418 selection call free supernatants were collected from the confluent monolayers and titreed on NIH 3T3 TK.sup.- cells as described above. The cell clones with the highest titre were chosen as PCLs and referred to as DA (D17 ampho), 2A (293 ampho), and CA (CF2 ampho), respectively. In no case was helper virus detected in the currently described PCLs, even when a retroviral vector (N2) which has a high probability of generating helper virus (Armentano et al., J. Virol. 62:1647-50, 1987) was introduced into the PCLs and the cells passaged for as long as 2 months (3 months for vector KT-3). On the other hand, the same vector introduced into the PA317 cell line generated helper virus within 3 weeks of continual passaging.

Detailed Description Text (368):
With respect to retroviral vector constructs carrying tissue (tumor)-specific promoters, biochemical markers with different levels of tissue-specificity are well known, and genetic control through tissue-specific promoters is understood in some systems. There are a number of genes whose transcriptional promoter elements are

relatively active in rapidly growing cells (i.e., transferrin receptor, thymidine kinase, etc.) and others whose promoter/enhancer elements are tissue specific (i.e., HBV enhancer for liver, PSA promoter for prostate). Retroviral vectors and tissue-specific promoters (present either as an internal promoter or within the LTR) which can drive the expression of selectable markers and cell cycle genes (i.e., drug sensitivity, Eco gpt; or HSVTK in TK-cells). Expression of these genes can be selected for in media containing mycophenolic acid or HAT, respectively. In this manner, tumor cells containing integrated provirus which actively expresses the drug resistance gene will survive. Selection in this system may involve selection for both tissue-specific promoters and viral LTRs. Alternatively, specific expression in tumor cells, and not in normal cells, can be counter-selected by periodically passaging virus onto normal cells, and selecting against virus that express Eco gpt or HSVtk (drug sensitivity) in those cells (by thioxanthine or acyclovir). Infected cells containing integrated provirus which express Eco gpt or tk phenotype will die and thus virus in that cell type will be selected against.

Detailed Description Text (385):
An example of a well-characterized housekeeping promoter is the HPRT promoter. HPRT is a purine salvage enzyme which expresses in all tissues. (See Patel et al., Mol. Cell Biol. 6:393-403, 1986 and Melton et al., Proc. Natl. Acad. Sci. 81:2147-2151, 1984). This promoter is inserted in front of various gag/pol fragments (e.g., Bal I/Sca I; Aat II/Sca I; Pst I/Sca I of MOMLV; see RNA Tumor Viruses 2, Cold Spring Harbor Laboratory, 1985) that are cloned in Bluescript plasmids (Strategene, Inc.) using recombinant DNA techniques (see Maniatis et al., Molecular Clonina: A Laboratorv Manual, Cold Spring Harbor, 1982). The resulting plasmids are purified (Maniatis et al., op. cit.) and the relevant genetic information isolated using Geneclean (Bio 101) or electroelution (see Hogan et al. (eds.), Manipulatina the Mouse Embryo: A Laboratory Manual, Cold Spring Harbor, 1986).

Detailed Description Paragraph Table (3):
TABLE 3 PROPERTIES OF MoMLV GAG/POL-EXPRESSING CELLS LARNL RT p30.sup.gag TITRE CELL NAME ACTIVITY (CPM) EXPRESSION (CFU/ML) 3T3 800 - N.D. PA317 1350 +/- 1.2 .times. 10.sup.3 D17 800 - N.D. D17 4-15 5000 +++++ 1.2 .times. 10.sup.4 D17 9020 2000 +++ 6.0 .times. 10.sup.3 D17 9-9 2200 ++ 1.0 .times. 10.sup.3 D17 9-16 6100 +++++ 1.5 .times. 10.sup.4 D17 8-7 4000 - N.D. HT1080 900 - N.D. HTSCV21 16400 +++++ 8.2 .times. 10.sup.3 HTSCV25 7900 +++ 2.8 .times. 10.sup.3 HTSCV42 11600 ++ 8.0 .times. 10.sup.2 HTSCV26 4000 - <10 293 600 - N.D. 293 2-3 6500 +++++ 7 .times. 10.sup.4 293 5-2 7600 +++++ N.D.

Other Reference Publication (108):
Overhauser et al., "Generation of Glucocorticoid-Responsive Moloney Murine Leukemia Virus by Insertion of Regulatory Sequences from Murine Mammary Tumor Virus into the Long Terminal Repeat," J. Virol., 54(1):133-144 (1985).

Other Reference Publication (115):
Shinnick et al., "Nucleotide Sequence of Moloney Murine Leukaemia Virus," Nature, 293:543-548 (1981).

Other Reference Publication (169):
Rein et al., "Myristylation Site in Pr65.sup.gag is Essential for Virus Particle Formation by Moloney Murine Leukemia Virus," Proc. Nat'l Acad. Sci., USA, 83:7246-7250 (Oct., 1986).

L10: Entry 5 of 18 File: USPT Dec 17, 2002

DOCUMENT-IDENTIFIER: US 6495349 B1
TITLE: Chimeric gene constructs

Detailed Description Text (202):
The insertion of retroviruses or retroviral vectors into the germ line of transgenic animals results in little or no expression. This effect, described by Jaenisch (see Jahner et al., Nature 298:623-628, 1982), is attributed to methylation of 5' retroviral LTR sequences. This technique would overcome the methylation effect by substituting either a housekeeping or tissue-specific promoter to express the retroviral vector/retrovirus. The U3 region of the 5' LTR, which contains the enhancer elements, is replaced with regulatory sequences from housekeeping or tissue-specific promoters (see FIG. 20). The 3' LTR is fully retained, as it contains sequences necessary for polyadenylation of the viral RNA and integration. As the result of unique properties of retroviral replication, the U3 region of the 5' LTR of the integrated provirus is generated by the U3 region of the 3' LTR of the infecting virus. Hence, the 3' is necessary, while the 5' U3 is dispensable. Substitution of the 5' LTR U3 sequences with promoters and insertion into the germ line of transgenic animals results in lines of animals capable of producing retroviral vector transcripts. These animals would then be mated to gag-pol-env animals to generate retroviral-producing animals (see FIG. 22).